II. REMARKS

A. Claim Status

Claims 26, 28-29, 32 - 34, 38, 39, 41, 43, 46- 47, 52 and 54, and new claims 55-68 are pending in the application.

Claims 1-16, 30and 36 have been previously cancelled.

Claims 17-25, 27, 31, 35, 37, 40, 42, 44, 45, 48-51 and 53 are cancelled by this amendment. Claims 38 and 46 are amended to correct minor grammatical errors. The amendments are editorial in nature and do not present new matter.

Claims 55-68 are added as new claims. The new claims are fully supported by the original specification. Support for all new claims is discussed in the section entitled "Support for New Claims." No new matter is introduced by this amendment.

B. Formal Matters Noted in the Office Action

In numbered item 1, the examiner indicates that the appropriate maintenance fee for the U.S. Patent No. 5,098,893 have been paid and therefore the reissue procedures are available for this patent. The paragraph requires no further comment.

In numbered item 2, the examiner indicates that the assent of the assignee under37 CFR 1.172 filed on October 3, 2002 is approved. The paragraph requires no further comment.

In numbered item 3, the examiner indicates that the original patent was surrendered during the prosecution of the parent reissue application 09/270,792.

In reply, the applicants note that this paragraph requires no further comment.

In numbered item 4, the examiner (1) reminds the applicants of the continuing duty of disclosure and (2) obligation to timely call to the attention of the office any prior or concurrent proceeding in which patent No. 5,098,893 is or was involved.

In reply, the applicants believe that all material information, including all relevant information regarding related proceedings, have been filed in the parent 09/290,791 application.

In numbered item 5, the examiner indicates that reissue declaration filed October 3, 2002 is approved.

In reply, the applicants note that this paragraph requires no further comment.

C. Items 6 and 7 in the Office Action - The Rejections of Claims 21, 31, 37-39, and 41 Under 35 USC 251 for New Matter

In numbered items 6 and 7, the examiner rejects claims 21, 31, 37-39, 41, 48 and 54 under 35 USC 251, stating that:

> The is no original disclosure supporting the exclusion of rennin as is recited in the instant claims 21, 31, 37, 39, and 41. Rennin is not mentioned in the disclosure, and silence in the specification is not support for a negative claim limitation. See Ex parte Grasselli, 231 USPQ 393, aff'd on reconsideration 231 USPQ 395 (Bd. App. 1983). Accordingly, the negative claim limitation in these claims constitute new matter. Claims 38, 48 and 54 recites dissolution in an aqueous solution having pH of about 7, which embraces dissolution at slightly acidic pHs. However, there is no original disclosure in the specification of dissolution at slightly acidic pHs, the only pHs recited in the section of the specification cited by Applicants ranging from 7.0 to 7.6. Accordingly, the pH range recited in claims 38, 48 and 54 is new matter. [Office Action page 3 line 20 to page 4 line 6.]

1. Reply to the Rejections of Claims 21, 31, 37, 39, and 41

In reply, the applicants respectfully disagree for the following reasons.

The applicants conceived of an invention generically applicable to produce storage stability by generating a glassy state. The subject matter defined by claims 21, 31, 37, 39, and 41 generically claims that invention, and specifically excludes rennin only because of the reference to rennin in the Shah reference. The applicants` admit that the specification of this application does not mention rennin. However, that does not mean that the applicant's were not in possession of the genus of the inventions claimed by claims 21, 31, 37, 39, and 41, either including or excluding rennin. The applicant respectfully submits that there is no rational basis for a rule of law precluding negative limitations that exclude a species anticipating a generic claim when the reference does not teach the generic utility of the claimed invention. That is the case here. To the extent case law is inconsistent with this reasoning, it should be overruled, with the USPTO's reliance upon Grasselli not withstanding.

Applicants position is supported by members of the patent bar, as indicated by the reasoning in the article by Mr. Harris Pitlick regarding the written description requirement, which was published in the Journal of the Patent Office Society. A copy of the article was enclosed in applicants' response dated October 3, 2002.

2. Reply to the Rejection of Claims 38, 48 and 54

In reply, the applicants respectfully disagree for the following reasons. As stated by the examiner, the specification discloses solutions having pH from 7.0 to 7.6. Explicit disclosure of solutions having pH 7.0 and slightly higher than 7.0 clearly provides adequate support for the claimed language "pH of about 7." While the phrase "about 7" is not verbatim disclosed in the original specification, the claimed invention does not have to be described literally in the specification to satisfy the description requirement. The claim language "about 7" is a mere rephrasing of what is explicitly disclosed in the specification. Therefore, the claimed phrase "pH of about 7" does not constitute new matter.

D. **Item 8 in the Office Action - The Rejections of Claims 21, 27-29, 31, 37 and 46 as Indefinite**

In item 8, the examiner rejects claims 21, 27-29, 31, 37 and 36 stating that:

> 8. Claims 21, 27-29, 31, 37 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Dependent claims 21, 31 and 37 recite that the biologically active material is not renin. However, the independent claims upon which these claims depend do not permit the biologically active material to be renin, either by narrowly defining the possible enzymes or by excluding enzymes as a whole from constituting the biologically active material. [Office action page line 19 to page 5 line 3.]

In response, the applicants note that claims 21, 31 and 37 are cancelled by this amendment and rejection of these claims is moot.

The examiner further rejects claim 46 stating that:

> Claim 46, lines 15-16, recites that the enzyme can comprise an enzyme. It is also unclear what "constitutes "restriction dehydrogenase enzymes." It is believed that at line 6, "restriction dehydrogenase enzymes" should be re-written as dehydrogenase enzymes, restriction enzymes." [Office action page 4 lines 4-7.]

In response, the applicants amended claim 46 as suggested by the examiner.

E. **Item 9 in the Office Action - The Objection to Claims 19-25, 38 and 45**

In item 9, the examiner objects to claims 19-25, 38 and 45, stating that:

> 9. Claim 18 is objected to because of the following informalities: At claims 38 and 45, second-to-last line of each claim, the semicolon after "dehydrogenase enzymes" should be changed to comma. [Office action page 4 lines 8-10.]

In response, the applicants have amended claim 38 to comply with the examiner's editorial requirement. Claim 45 is cancelled by ths amendment.

F. **Item 10 of the Office Cation - objection of claims 38 and 48; and 49 and 50 as being identical in scope**

In item 10, the examiner objects to claims 38 and 48, and claims 49 and 50 as identical in scope.

In reply applicants note that claims 48, 49 and 50 are cancelled by this amendment. Therefore the rejection of these claims is moot.

G. **Items 11-13 of the Office Action - The Rejections and Provisional Rejection of Claims 26-29, 31-35, 37-44 and 45-54 for Obviousness-type Double Patenting**

In items 21 and 13, the examiner rejects claims 26-29, 31-35, 37-44 and 45-54 for obviousness-type double patenting, stating that:

> 11. Claims 26-29, 31-35, 37-44 and 45-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-94 of U.S. Reissue patent No. 37,872 (which issued based upon reissue Application No. 09/270,791. [Office action page 5 lines 6-8.]
>
> 12. Claims 26-29, 31-35, 37-44 and 45-54 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over all of the claims of co-pending Application No. 09/939,688. [Office action page 5 lines 21-23.]

In reply, the applicant disagrees that the claims in the instant application are properly rejected as being unpatentable over claims 1-94 of the US Reissue patent No. 37,872. However, to expedite the prosecution of this application applicants file a terminal disclaimer over the referenced patent concurrently herewith. [1]

The rejection over application No. 09/939,688 is merely <u>provisional</u> rejection because this application is still pending. The applicants will consider how to respond to the provisional double patenting rejections either when the rejection is not provisional or when this application is otherwise in condition for allowance, i.e., when the issue is ripe for action.

H. **Items 14- 15 of the Office Action - The Rejections of Claims 26, 28-29, 31, 43, 46 and 52 as Anticipated by Koyama et al.**

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[1] A Terminal Disclaimer over Re. 37, 872 is attached hereto.

In item 15, the examiner rejects claims 26, 28-29, 31, 43, 46 and 52, stating that:

> 15. Claims 26, 28, 29, 31, 43, 46 and 52 are rejected under 35 U.S.C. 102(e) as Koyama et al. Koyama et al teach stabilized water-soluble dry solid compositions comprising proteinaceous bioactive substances, for example hormones. Aqueous solutions of the proteinaceous bioactive substances are combined with aqueous solutions a polysaccharide composed mainly of maltotriose units at a ratio of polysaccharide:protein of preferably 1 to 10,000. The weight ratio of the polysaccharide to the substance is at least 0.5, preferably from 1.0 to 10000. The combined solutions are then dried, either by conventional procedures at reduced pressure and a temperature below 30°C, or else by freeze-drying. In one series of examples, greater than 90% of activity is retained after storage at 37°C for one month, which is consistent with Applicants' requirement for at least 53% retained activity after storage for 8 weeks at 25°C. The dry solid can be formed into a tablet. See, e.g., the Abstract; column 2, lines 10-24 and 38-66; Experiment 3; and the Examples. In view of the similarity in the components of the compositions and the retained activity of the compositions, the compositions of Koyama et al are deemed inherently to have the same storage stability and T_g claimed by Applicants and are deemed to anticipate the compositions claimed by Applicants. Sufficient evidence of similarity between the compositions of Koyama et al and Applicants' claimed compositions is deemed to be present to shift the burden to Applicants to show that their claimed compositions are unobviously different than those of Koyama et al. Note that even a patentable difference in the process of making does not necessarily impart patentability to product-by-process claims where the product is otherwise anticipated by the prior art. [Office action page 6 line 17 to page 7 line 14.]

In reply, the applicants first note that the Koyama et al. patent does not disclose the actual state of the resulting compositions. It refers to freeze drying for all of its experiments and examples (see column 3 line 44 (experiment 1-A); column 5 line 13 (experiment 2-B); column 5 line 58 (experiment 3); column 6 lines 45-46 (example 1); (column 6 line 63 (example 2); column 7 line 12 (example 3); column 7 line 48 (example 4); column 8 line 12 (example 5); column 8 lines 56-57 (example 6); and column 9 line 37 (example 7)), but it does not disclose any freeze drying conditions.

The examiner concludes that, in "view of the similarity in the components of the composition and retained activity of the compositions, the compositions of Koyama et al. are deemed inherently to have the same storage stability, and Tg claimed by Applicants".

In reply, the applicants point out that this conclusion is inconsistent with the complete teachings of the Koyama et al. patent.

The Koyama et al. patent teaches that stabilizers *other than a polysaccharide mainly composed of maltotriose units* do ***not*** provide desired high stability. See, for example, Table 1 in columns 3-4 (indicating that various possible stabilizers, except for specific polysaccharides do not retain desired activity of the active substance in the dried state.)

The drying conditions of the Koyama et al.'s samples formed from the stabilizers that do not provide storage stability, and the drying conditions of samples containing the polysaccharide mainly composed of maltotriose units that do provide storage stability, are not explicitly stated. However, the clear implication of the Koyama et al. patent's describing the samples containing the polysaccharide mainly composed of maltotriose units as providing an unexpected satisfaction ("unexpectedly satisfying"; column 2 lines 1-2) of the retention stability requirement is that the drying conditions *were the same* for the failed and the successful stabilizers, implying that those drying conditions were *freeze drying* conditions.

The Koyama et al. patent discloses that ineffective stabilizers ***do not*** provide storage stability when dried under impliedly the same drying conditions (impliedly freeze drying conditions) as Koyama et al.'s inventive polysaccharides. This fact indicates that the Koyama et al.'s drying conditions *did not* result in glassy state compositions. If Koyama et al.'s drying conditions resulted in the glassy state, all of Koyama et al.'s samples would have been stabilized, as taught by Dr. Franks et al. in this application. Failure of Koyama et al.'s ineffective stabilizers to provide storage stability indicates that compositions containing those ineffective stabilizers were not in a glassy state. In particular, ***dextran*** is disclosed in the Koyama et al. patent as an ineffective stabilizer. As disclosed in the Koyama et al patent, compositions stabilized with ***dextran*** retained only 65.3 % and 81.5 % activity after being stored for two months at 37 ^{o}C and 4^{o}C, respectively. In contrast, this application discloses that compositions comprising ***dextran*** as the carrier substance dried according to the method of the invention disclosed in this application exhibit greater than 91 % activity when stored at 25 ^{o}C for 8 and 10 weeks, respectively. This exceeds activity the compositions disclosed in the Koyama et al patent stored for the same period of time. This application shows in example 13, in the table in column 13, that dextran is an effective stabilizer when existing in a glassy state composition. This application teaches broadly (column 2 lines 24-29) that it is the existence of the glassy state that is important for storage stability. The only reasonable

conclusion to draw from these facts is that Koyama et al.'s dextran containing samples were not in a glassy state. The logical extension of that conclusion is that Koyama et al.'s inventive compositions were dried under the same conditions as Koyama et al.'s dextran samples and therefore had the same residual water concentration, and therefore that those compositions were too high in water concentration to be in a glassy state.

Therefore, the examiner's conclusion that the similarity in the components of the compositions and the retained activity of Koyama et al. inventive compositions is prima facie evidence that those composition were in a glassy state is inconsistent with the entire teachings of the Koyama et al. patent.

Hence, considering all of what Koyama et al. teaches, instead of just what Koyama et al. teaches regarding the polysaccharide mainly composed of repeating maltotriose units, indicates that the drying conditions used by Koyama et al. did not result in compositions in a glassy state, and indicates that the examiner's conclusion that "similarity in ... retained activity between Koyama et al's products and Applicants' claimed products" is not "evidence that Koyama et al.'s freeze dried material existed in a glassy state."

Accordingly, the anticipation rejections of claims 26, 28-31, and 43 based upon the Koyama et al. patent are improper and therefore should be withdrawn.

I. Item 16 of the Office Action - The Rejections of Claims 32-34, 37 and 47 for Obviousness over Koyama in View of Applicants' Admission

The office action states that:

> 16. Claims 32-34, 37 and 47 are rejected under 35 U.S.C. 103(a) as being obvious over Koyama et al as applied against claims 26, 28-31 and 43 above, and further in view of Applicants' admission of the prior art at column 1, lines 59-62; column 4, lines 57 - 66; and column 5, lines 3-8. Koyama et al do not teach any examples in which conventional drying procedures at reduced pressure and a temperature below 30°C are used. However, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the dried compositions of Koyama et al using conventional drying procedures at reduced pressure and at a temperature below 30°C because as admitted by Koyama et al, such drying procedures are conventional and are suitable for producing Koyama et al's desired products, and because as admitted by Applicants at column 1, lines 59-62, of the application, freeze-drying is costly in capital and energy and is irreproducible. Regardless of the method used to produce the dried compositions of Koyama et al, the dried compositions of Koyama et al would have been expected to

> have a T_g greater than 20°C because as admitted by Applicants at column 4, lines 59-60, the Tg for maltotriose is 76°C and as admitted by Applicants at column 5, lines 3-8, the T_g for water-soluble or water-swellable synthetic polymers is a function of molecular weight. Accordingly, the T_g for Koyama et al's polysaccharide composed mainly of maltotriose units would have been expected to be even higher than the 76°C for a maltotriose monomer. The T_g for Koyama et al's proteinaceous bioactive substances would also have been expected to be relatively high because the proteins are also water-soluble polymers of relatively high molecular weight. Even if Koyama et al's dried compositions were to contain several percent residual water after drying, in view of Applicants' admitted rule-of-thumb at column 4, lines 63-65, of an approximately 6°C decrease in T_g for each percent of moisture added, the dried compositions would still have a T_g greater than 20°C in view of the relatively high T_g of the major components. [Office action page 7 line 15 to page 8 line 16.]

In reply, the applicants respectfully dispute the conclusion that "it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the dried compositions of Koyama et al. using conventional drying procedures at reduced pressure and at a temperature below 30°C." For one thing, Koyama et al. did not indicate in the Koyama et al. patent, that they actually did that.

Moreover, in 1989, there were no non-freeze drying "conventional drying procedures carried out at a reduced pressure and temperature below 30 °C" (quoting the Koyama et al. patent column 2 lines 52-54) used on proteinaceous bioactive compounds. See Second Franks Declaration dated October 2, 2000 and submitted in the parent application S.N. 09/270,791[2]. Hence, what procedure Koyama et al. was referring to is vague.

One of ordinary skill in the art in 1989 reading the Koyama et al. patent would have recognized the non-freeze drying language (column 2 lines 52 - 55) as mere surplusage unsupported by any experimental results or process conditions, and therefore would not have been motivated to dry without freeze drying. Moreover, one of ordinary skill in the art in 1989 would have believed that drying purified biologically active samples without first freezing them would destroy an unacceptably large fraction of their activity. Second Franks Declaration.

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[2] A copy of the Second Franks Declaration was provided with the previous reply dated October 3, 2002.

Even assuming for the sake of argument one of ordinary skill in the art in 1989 was in fact motivated to dry an aqueous unstable material without freeze drying, there was no teaching suggesting using the degree of drying required to obtain a composition that is in a glassy state when existing at 20° C. Because those skilled in the art did not know that the amount of residual water was significant, it is likely that following Koyama et al.'s suggestion to experiment with non-freeze drying would not have resulted in a glassy state material.

At best, the passage in the Koyama et al. patent's reference to a non-freeze drying process (column 2 lines 52-55) was a motivation to experiment since (1) it did not identify any process conditions relating to the reduced pressure and temperature (e.g., time of reduced pressure and heat energy to be input to maintain temperature above freezing) that would have resulted in a dry solid containing a proteinaceous bioactive substance (Koyama et al. column 1 lines 9-12) and (2) it did not relate those process conditions to what was required to achieve the intended stability. In hindsight, to apply the column 2 lines 52-55 statement would probably have required (1) determining process conditions resulting in reduced pressure while maintaining temperature between freezing and 30 °C, (2) determining a relationship between long term storage stability and those process conditions by long term storage testing, and (3) identifying from the relationship whether, and under what conditions, if any, long term storage stability could be obtained. Merely providing a motivation to experiment is an insufficient legal basis to maintain an obviousness rejection. In re Dow Chemical Co., 5 USPQ2d 1529, 1532 (Fed. Cir. 1988)("The PTO presents, in essence, an 'obvious to experiment' standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure." Emphasis supplied.) The Koyama et al. patent, at best, provides a motivation to experiment. Therefore, it is not a proper basis for an obviousness rejection.

Moreover, since Koyama et al. did not provide any indication that processing at a reduced pressure and at temperatures between freezing and 30 °C would actually result in a stabilized water soluble dry solid containing proteinaceous bioactive substance, there was no reasonable expectation of success. Both a suggestion to try and a reasonable expectation of

success must be present for an obviousness rejection to be maintained. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991) ("Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion *and the reasonable expectation of success must be founded in the prior art*, not in the applicant's disclosure. Id." Emphasis supplied.) The Koyama et al. patent provides at best a motivation to experiment, not a suggestion to try a specified processing procedure. Moreover, it provides no reasonable expectation of success for a non-freeze dried procedure. For both of these reasons, the obviousness rejections based upon the teachings of Koyama et al. are improper and should be withdrawn.

Moreover, for the reasons presented above in the discussions of the anticipation rejections based upon the Koyama et al. patent, the Koyama et al. patent does not inherently disclose a composition that is in a glassy state at 20° C. Even assuming arguendo that the prior art motivated drying aqueous unstable materials without freeze drying, there is no teaching suggesting using the degree of drying required to obtain a composition that is in a glassy state when existing at 20° C. Moreover, the most logical conclusion is that utilizing drying conditions other than freeze drying, one of ordinary skills in the art would aim at obtaining compositions exhibiting properties as close to the properties of the compositions disclosed in the Koyama et al. patent as possible to obtain satisfactory storage stable compositions. Therefore, following teachings of the Koyama et al patent an ordinary artisan would be motivated to obtain compositions that are too high in water concentration to be in a glassy state, as disclosed in the Koyama et al. patent.

Accordingly, the teachings of the Koyama et al. patent neither alone nor in combination with applicants' admission suggest the claimed invention and obviousness rejections of claims 32-34, 37, and 47 based upon the Koyama et al. patent in view of applicants' admission should be withdrawn.

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I. **Support for New Claims**

CLAIM NUMBER	CITATION TO SUPPORT IN ORIGINAL PATENT
55. A method of rendering a purified biologically active material storage-stable at 20° C and pharmacologically using said material, which material is unstable in aqueous solution at 20° C, comprising the steps of: (1) dissolving to form an aqueous solution of	Claim 12. Claim 12, column 2 lines 50-54
(a) a purified biologically active material (i) which is unstable in aqueous solution at 20° C and which is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto and (ii) which is not an enzyme and (b) a carrier substance that is water-soluble or water-swellable;	Claim 12, claim 2; and column 2 lines 30-36 and line 51-52 and column 3 lines 1-13.
(2) forming said solution into a glassy state composition by evaporating liquid water, wherein said glassy state composition exists when at 20° C; and	Claim 12, column 2 lines 50-54, and column 6 lines 37-47.
(3) administering said purified biologically active material stored in said glassy state composition.	Column 1 line 4.

56. The method of claim 55 wherein said purified biologically active material is selected from the group consisting of immunoglobulin, an enzyme cofactor, a nucleoside, a nucleotide, a dinucleotide, a dimer of a nucleoside, a dimer of a nucleotide, an oligomer of a nucleoside, and an oligomer of a nucleotide.	Claim 12, claim 2; and column 2 lines 30-36 and line 51-52 and column 3 lines 1-13.
57. The method of claim 55 wherein said purified biologically active material is selected from the group consisting of a hormone, a transport protein, a blood clotting factor, enzyme cofactor, a pharmacologically active protein, a transport protein, and a blood clotting factor.	Claim 12, claim 2; and column 2 lines 30-36 and line 51-52 and column 3 lines 1-13.
58. The method of claim 55 wherein said purified biologically active material is a hormone.	Claim 12, claim 2; and column 2 lines 30-36 and line 51-52 and column 3 lines 1-13.
59. The method of claim 55 wherein said purified biologically active material is an immunoglobulin.	Claim 12, claim 2; and column 2 lines 30-36 and line 51-52 and column 3 lines 1-13.
60. The method of claim 55 wherein said purified biologically active material is a blood clotting factor.	Claim 12, claim 2; and column 2 lines 30-36 and line 51-52 and column 3 lines 1-13.
61. The method of claim 55 wherein said purified biologically active material is a pharmacologically active protein.	Claim 12, claim 2; and column 2 lines 30-36 and line 51-52 and column 3 lines 1-13.
62. The method of claim 55 further comprising the step of shaping said glassy state composition.	Column 5 lines 41-42.
63. The method of claim 62 wherein said step of shaping comprises compressing said glassy state composition into a tablet.	Column 5 lines 41-42.

64. A method of rendering a purified biologically active material storage-stable at 20° C, which material is unstable in aqueous solution at 20° C, comprising the steps of: (1) dissolving to form an aqueous solution of (a) a purified biologically active material, which is unstable in aqueous solution at 20° C and which is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto and (b) a carrier substance that is water-soluble or water-swellable; (2) evaporating liquid water from said solution, thereby converting said solution to a glassy state composition, wherein said glassy state composition exists when at 20° C;	Support for limitations shown for previous claims.
wherein said evaporating is done without heating; and	Claim 12, column 2 lines 50-54, and column 6 lines 24-25.
wherein said purified biologically active material is selected from the group consisting of immunoglobulin, an enzyme cofactor, a nucleoside, a nucleotide, a dinucleotide, a dimer of a nucleoside, a dimer of a nucleotide, an oligomer of a nucleoside, and an oligomer of a nucleotide.	Support for limitations shown for previous claims.

65. A method of rendering a purified biologically active material storage-stable at 20° C, which material is unstable in aqueous solution at 20° C, comprising the steps of: (1) dissolving to form an aqueous solution of (a) a purified biologically active material which is unstable in aqueous solution at 20° C and which is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto and (b) a carrier substance that is water-soluble or water-swellable; (2) evaporating liquid water from said solution thereby converting said solution into a glassy state composition, wherein said glassy state composition exists when at 20° C; wherein said evaporating is done without heating; and wherein said purified biologically active material is selected from the group consisting of a hormone, immunoglobulin, a transport protein, a blood clotting factor, a pharmacologically active protein, a dehydrogenase, restriction enzyme, an oxidase enzyme, a reductase enzyme, a transport protein, and a blood clotting factor.	Support for limitations shown for previous claims.

66. A method of rendering a purified biologically active material storage-stable at 20° C, which material is unstable in aqueous solution at 20° C, comprising the steps of: (1) dissolving to form an aqueous solution of (a) a purified biologically active material which is unstable in aqueous solution at 20° C and which is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto and (b) a carrier substance that is water-soluble or water-swellable; (2) evaporating liquid water from said solution, thereby converting said solution into a glassy state composition, wherein said glassy state composition exists when at 20° C; wherein said evaporating is done without heating; and wherein said carrier substance comprises a member of the group consisting of a polysaccharide, a disaccharide, and a sugar that has a Tg of at least 55° C and not greater than 150° C.	Support for limitations shown for previous claims.

67. A glassy state composition which is storage-stable at 20° C, comprising: (1) a carrier substance which is water-soluble or water-swellable; (2) at least one material to be stored which is dissolved in said carrier substance; wherein said glassy state composition including said carrier substance has the property of being in a glassy state and being storage stable when at 20° C; wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution when at 20° C and is selected from the group consisting of immunoglobulin, an enzyme cofactor, a nucleoside, a nucleotide, a dinucleotide, a dimer of a nucleoside, a dimer of a nucleotide, an oligomer of a nucleoside, and an oligomer of a nucleotide.	Support for limitations shown for previous claims.
68. A method of forming a glassy state composition which is storage-stable at 20° C, comprising the steps of: (1) dissolving to form an aqueous solution of (a) at least one material to be stored and (b) a carrier substance which is water-soluble or water-swellable; (2) evaporating water from said solution, thereby forming said glassy state composition; wherein said glassy state composition including said carrier substance has the property of being in said glassy state and being storage stable when at 20° C; wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution when at 20° C and is selected from the group consisting of immunoglobulin, an enzyme cofactor, a nucleoside, a nucleotide, a dinucleotide, a dimer of a nucleoside, a dimer of a nucleotide, an oligomer of a nucleoside, and an oligomer of a nucleotide.	Support for limitations shown for previous claims.

J. **Conclusion**

In view of the foregoing comments, the applicants submit that this application is now in condition for allowance pending resolution of the provisional double patenting rejection issues. The examiner is urged to contact the undersigned by telephone at 703-415-0012 if that will expedite allowance of this application.

Respectfully Submitted,

4-3-2003
Date

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III. **APPENDIX**

Marked up version of Claims for Amendment in Response to December 4, 2002 Office Action

Claims 1-16. Cancelled by amendment filed February 19, 2002.

Claims 30 and 36. Cancelled by amendment filed October 3, 2002.

Claims 26, 28-29, 32-34, 38, 39, 41, 43, 46- 47, 52, 54, and 55-68 are currently pending, claims 17-25, 27, 31, 35, 37, 40, 42, 44, 45, 49-51 and 53 cancelled by this amendment.

Rejected over Koyama 26. (Previously Amended) A glassy state composition which is storage-stable at 20° C, comprising:

(1) a carrier substance which is water-soluble or water-swellable and

(2) at least one material to be stored which is dissolved in said amorphous carrier substance;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said purified biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto;

wherein said composition has the properties that it is storage stable and exists in a glassy state when at 20° C;

wherein a weight ratio of said purified biologically active material to said carrier substance is between about 2:1 and about 1:1; and

wherein said biologically active material is not an enzyme.

Rejected over Koyama 28. (Previously Amended) The composition of claim 46 wherein said ratio is about 2:1.

Rejected over Koyama 29. (Previously Amended) The composition of claim 46 wherein said ratio is about 1:1.

Rejected over Koyama+ Admission 32. (Previously Amended) A method of rendering a material storage stable at 20° C which material is unstable in aqueous solution at room temperature of 20° C, comprising the steps of:

(1) dissolving to form an aqueous solution

(a) said material and

(b) a carrier substance which is water-soluble or water-swellable;

(2) evaporating liquid water from said solution thereby converting said solution into a glassy state composition;

wherein said material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto;

wherein said composition has the property that it is storage stable and exists in said glassy state when at 20° C; and

wherein a weight ratio of said purified biologically active material to said carrier substance is between about 1:2 and about 1:1; and

wherein said biologically active material is not an enzyme.

Rejected over Koyama+ Admission 33. (Previously Amended) The method of claim 47 wherein said weight ratio is about 1:1.

Rejected over Koyama+ Admission 34. (Previously Amended) The method of claim 47 wherein said weight ratio is about 1:2.

Rejected as containing New Matter; Allowable over art 38. (Amended) A method of forming a composition which is storage-stable at 20° C, said composition comprising:

(1) dissolving to form an aqueous solution

(a) a carrier substance which is water-soluble or water-swellable and

(b) at least one material to be stored;

(2) forming said solution containing said carrier substance with said at least one material dissolved therein into a glassy state by evaporation of liquid water to produce said composition;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said purified biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto; and

wherein said composition contains no more than 4 percent by weight of water; and

wherein said composition has the properties that it is storage stable and exists in a glassy state when at 20° C; and

wherein said step of dissolving comprises dissolving in an aqueous solution having a pH of about 7;

with proviso that when said at least one material comprises an enzyme, said enzyme comprises an enzyme selected from dehydrogenase enzymes[;], restriction enzymes, oxidase enzymes, and reductase enzymes.

Rejected as containing New Matter; Allowable over art 39. A composition which is storage-stable at 20° C, comprising:

(1) a carrier substance which is water-soluble or water-swellable and is in a glassy state;

(2) at least one material to be stored which is dissolved in said carrier substance;

wherein said composition exists in a glassy state at 20° C;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said purified biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto;

wherein said composition contains no more than 4 percent by weight of water; and

wherein said biologically active material is not rennin.

Rejected as containing New Matter; Allowable over art 41. A composition which is storage-stable at 20° C, comprising:

(1) a carrier substance which is water-soluble or water-swellable and

(2) at least one material to be stored which is dissolved in said carrier substance;

wherein said composition has the property that it exists in a glassy state when at 20° C;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto;

wherein said composition contains no more than 4 percent by weight of water; and

wherein said biologically active material is not rennin.

Rejected over Koyama 43. (Previously Amended) A composition which is storage-stable at 20° C, comprising:

(1) a carrier substance which is water-soluble or water-swellable and

(2) at least one material to be stored which is dissolved in said carrier substance;

wherein said composition has the property that it exists in a glassy state when at 20° C;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto; and

wherein said biologically active material is not an enzyme and is not freeze stable.

Rejected over Koyama 46. **(Amended)** A glassy state composition which is storage-stable at 20° C, comprising:

(1) a carrier substance which is water-soluble or water-swellable and

(2) at least one material to be stored which is dissolved in said amorphous carrier substance;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said purified biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto;

wherein said composition has the properties that it is storage stable and exists in a glassy state when at 20° C;

wherein a weight ratio of said purified biologically active material to said carrier substance is between about 2:1 and about 1:1;

with proviso that when said at least one material comprises an enzyme, said enzyme comprises an enzyme selected from restriction enzymes, dehydrogenase enzymes, [enzymes] oxidase enzymes, and reductase enzymes.

Rejected over Koyama+ Admission 47. A method of rendering a material storage stable at 20° C which material is unstable in aqueous solution at room temperature of 20° C, comprising the steps of:

(1) dissolving to form an aqueous solution

(a) said material and

(b) a carrier substance which is water-soluble or water-swellable;

(2) evaporating liquid water from said solution thereby converting said solution into a glassy state composition;

wherein said material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto;

wherein said composition has the property that it is storage stable and exists in said glassy state when at 20° C; and

wherein a weight ratio of said purified biologically active material to said carrier substance is between about 1:2 and about 1:1;

with proviso that when said at least one material comprises an enzyme, said enzyme comprises an enzyme selected from restriction enzymes, oxidase enzymes, and reductase enzymes.

Rejected over Koyama 52. A composition which is storage-stable at 20° C, comprising:

(1) a carrier substance which is water-soluble or water-swellable and

(2) at least one material to be stored which is dissolved in said carrier substance;

wherein said composition has the property that it exists in a glassy state when at 20° C;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto; and

wherein said biologically active material is not freeze stable; and

with proviso that when said at least one material comprises an enzyme, said enzyme comprises an enzyme selected from dehydrogenase enzymes, restriction enzymes, oxidase enzymes, and reductase enzymes.

Rejected as containing New Matter; Allowable over art 54. A method of forming a composition which is storage-stable at 20° C, said composition comprising:

(1) dissolving to form an aqueous solution

(a) a carrier substance which is water-soluble or water-swellable and

(b) at least one material to be stored;

(2) forming said solution containing said carrier substance with said at least one material dissolved therein into a glassy state by evaporation of liquid water to produce said composition;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution at 20° C;

wherein said purified biologically active material is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto; and

wherein said composition contains no more than 4 percent by weight of water; and

wherein said composition has the properties that it is storage stable and exists in a glassy state when at 20° C; and

wherein said step of dissolving comprises dissolving in an aqueous neutral or slightly basic solution having a pH of about 7.

Claims 55 - 68 are added as NEW claims:

Rejected over Koyama+ Admission as indicated in 09/939,688. 55. (NEW. *Corresponds to claim 46 of '688 application*) A method of rendering a purified biologically active material storage-stable at 20° C and pharmacologically using said material, which material is unstable in aqueous solution at 20° C, comprising the steps of:

(1) dissolving to form an aqueous solution of

(a) a purified biologically active material (i) which is unstable in aqueous solution at 20° C and which is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto and (ii) which is not an enzyme and

(b) a carrier substance that is water-soluble or water-swellable;

(2) forming said solution into a glassy state composition by evaporating liquid water, wherein said glassy state composition exists when at 20° C; and

(3) administering said purified biologically active material stored in said glassy state composition.

Rejected over Koyama+ Admission as indicated in 09/939,688. 56. (NEW. *Corresponds to claim 48 of '688 application*) The method of claim 55 wherein said purified biologically active material is selected from the group consisting of immunoglobulin, an enzyme cofactor, a nucleoside, a nucleotide, a dinucleotide, a dimer of a nucleoside, a dimer of a nucleotide, an oligomer of a nucleoside, and an oligomer of a nucleotide.

Rejected over Koyama+ Admission as indicated in 09/939,688. 57. (NEW. *Corresponds to claim 49 of '688 application*) The method of claim 55 wherein said purified biologically active material is selected from the group consisting of a hormone, a transport protein, a blood clotting factor, enzyme cofactor, a pharmacologically active protein, a transport protein, and a blood clotting factor.

Rejected over Koyama+ Admission as indicated in 09/939,688. 58. (NEW. *Corresponds to claim 50 of '688 application*) The method of claim 55 wherein said purified biologically active material is a hormone.

Rejected over Koyama+ Admission as indicated in 09/939,688. 59. (NEW. *Corresponds to claim 51 of '688 application*) The method of claim 55 wherein said purified biologically active material is an immunoglobulin.

Rejected over Koyama+ Admission as indicated in 09/939,688. 60. (NEW. *Corresponds to claim 52 of '688 application*) The method of claim 55 wherein said purified biologically active material is a blood clotting factor.

Rejected over Koyama+ Admission as indicated in 09/939,688. 61. (NEW. *Corresponds to claim 53 of '688 application*) The method of claim 55 wherein said purified biologically active material is a pharmacologically active protein.

Rejected over Koyama+ Admission as indicated in 09/939,688. 62. (NEW. *Corresponds to claim 55 of '688 application*) The method of claim 55 further comprising the step of shaping said glassy state composition.

Rejected over Koyama+ Admission as indicated in 09/939,688. 63. (NEW. *Corresponds to claim 56 of '688 application*) The method of claim 62 wherein said step of shaping comprises compressing said glassy state composition into a tablet.

Rejected over Koyama+ Admission as indicated in 09/939,688. 64. (NEW. *Corresponds to claim 58 of '688 application*) A method of rendering a purified biologically active material storage-stable at 20° C, which material is unstable in aqueous solution at 20° C, comprising the steps of:

(1) dissolving to form an aqueous solution of

(a) a purified biologically active material, which is unstable in aqueous solution at 20° C and which is selected from the group consisting of peptides, proteins,

nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto and

(b) a carrier substance that is water-soluble or water-swellable;

(2) evaporating liquid water from said solution, thereby converting said solution to a glassy state composition, wherein said glassy state composition exists when at 20° C;

wherein said evaporating is done without heating; and

wherein said purified biologically active material is selected from the group consisting of immunoglobulin, an enzyme cofactor, a nucleoside, a nucleotide, a dinucleotide, a dimer of a nucleoside, a dimer of a nucleotide, an oligomer of a nucleoside, and an oligomer of a nucleotide.

Rejected over Koyama+ Admission as indicated in 09/939,688. 65. (NEW. *Corresponds to claim 59 of '688 application*) A method of rendering a purified biologically active material storage-stable at 20° C, which material is unstable in aqueous solution at 20° C, comprising the steps of:

(1) dissolving to form an aqueous solution of

(a) a purified biologically active material which is unstable in aqueous solution at 20° C and which is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto and

(b) a carrier substance that is water-soluble or water-swellable;

(2) evaporating liquid water from said solution thereby converting said solution into a glassy state composition, wherein said glassy state composition exists when at 20° C;

wherein said evaporating is done without heating; and

wherein said purified biologically active material is selected from the group consisting of a hormone, immunoglobulin, a transport protein, a blood clotting factor, a pharmacologically active protein, a dehydrogenase, restriction enzyme, an oxidase enzyme, a reductase enzyme, a transport protein, and a blood clotting factor.

Rejected over Koyama+ Admission as indicated in 09/939,688. 66. (NEW. *Corresponds to claim 60 of '688 application*) A method of rendering a purified biologically active material storage-stable at 20° C, which material is unstable in aqueous solution at 20° C, comprising the steps of:

(1) dissolving to form an aqueous solution of

(a) a purified biologically active material which is unstable in aqueous solution at 20° C and which is selected from the group consisting of peptides, proteins, nucleosides, nucleotides, dimers or oligomers of nucleosides or nucleotides, enzymes, enzyme cofactors and derivatives of any of the foregoing, said derivatives having one or more additional moieties bound thereto and

(b) a carrier substance that is water-soluble or water-swellable;

(2) evaporating liquid water from said solution, thereby converting said solution into a glassy state composition, wherein said glassy state composition exists when at 20° C;

wherein said evaporating is done without heating; and

wherein said carrier substance comprises a member of the group consisting of a polysaccharide, a disaccharide, and a sugar that has a Tg of at least 55° C and not greater than 150° C.

Rejected over Koyama+ Admission as indicated in 09/939,688. 67. (NEW. *Corresponds to claim 61 of '688 application*) A glassy state composition which is storage-stable at 20° C, comprising:

(1) a carrier substance which is water-soluble or water-swellable;

(2) at least one material to be stored which is dissolved in said carrier substance;

wherein said glassy state composition including said carrier substance has the property of being in a glassy state and being storage stable when at 20° C;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution when at 20° C and is selected from the group consisting of immunoglobulin, an enzyme cofactor, a nucleoside, a nucleotide, a dinucleotide, a dimer of a nucleoside, a dimer of a nucleotide, an oligomer of a nucleoside, and an oligomer of a nucleotide.

Rejected over Koyama+ Admission as indicated in 09/939,688. 68. (NEW. *Corresponds to claim 62 of '688 application*) A method of forming a glassy state composition which is storage-stable at 20° C, comprising the steps of:

(1) dissolving to form an aqueous solution of (a) at least one material to be stored and (b) a carrier substance which is water-soluble or water-swellable;

(2) evaporating water from said solution, thereby forming said glassy state composition;

wherein said glassy state composition including said carrier substance has the property of being in said glassy state and being storage stable when at 20° C;

wherein said at least one material comprises a purified biologically active material that is unstable in aqueous solution when at 20° C and is selected from the group consisting of immunoglobulin, an enzyme cofactor, a nucleoside, a nucleotide, a dinucleotide, a dimer of a nucleoside, a dimer of a nucleotide, an oligomer of a nucleoside, and an oligomer of a nucleotide.